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Lymphadenopathy Associated with COVID-19 Vaccination Mimicking Breast Cancer Related Axillary LAP: Imaging Findings Review of 880 Cases

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ABSTRACT

Background: With an increasing rate of lymphadenopathies (LAP) reported following COVID-19 vaccination with various vaccines, which can mimic breast cancer (BC), a comprehensive review, can disclose some practical information about BC workup that reduces the incidence and mortality of the disease along with unnecessary steps.

Methods: We conducted a literature search in online databases, including Scopus, Medline (PubMed), Web of Science, Embase (Elsevier), Cochrane library, and Google Scholar. Keywords of literature search included "COVID-19", "coronavirus disease", "Vaccine", and "Vaccination", "LAP", "Adverse event*", "Lymph node", "Cancer, breast", and "Lymphadenopathy".

Results: In total, 59 studies (n=880 cases), including 412 (46.8%) females, 146 (16.6%) males, and 322 (36.6%) cases with unknown gender were reviewed. We reviewed the LAP presentation after vaccination of the first or second dosage of Pfizer-BioNTech (n=754, 85.7%), Moderna (n=38, 4.3%), Oxford-AstraZeneca (n=39, 4.4%), Sputnik V (n=1, 0.1%), Johnson & Johnson/Janssen (n=1, 0.1%), and CureVac (n=1, 0.1%). In 46 (5.3%) cases, the type of vaccine was not reported. The most common LAP locations were axillary (n=540), followed by axillary and supraclavicular (n=271). We found that imaging findings of LAP associated with vaccination were seen from the first day to two months after vaccination of the first or second dosage of different types of COVID-19 vaccines.

Conclusion: This review study can draw a broad perspective by focusing on patients with cancer, especially BC, for clinicians to proceed with the right approach at the right time without additional invasive measures and not to delay the necessary measures in high-risk patients at the same time.

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INTRODUCTION

Following the COVID-19 pandemic and the resulting health challenges and mortality, multiple proceedings to solve the problem were proposed and tested. Notwithstanding efforts of the governments and health workers, official WHO statistics about patients and deaths numbers were a sign of their failed efforts to overcome the problem. The final solution should present a plan to stop the spread and increase the defense of people against the pathogenicity of the virus.[1-5] Finally, on the anniversary of the onset of the outbreak in December 2020, the first vaccine was approved for injection, as other vaccines with various mechanisms were made available for use over time. Therefore, vaccination began and continues at different rates among people worldwide. By May 25, 2021, about half of the U.S. population had received one or more doses.[6,7]

Along with all the advantages of the vaccines, gentle side effects including local pain at the injection site, fatigue, headache, muscle or joint pain, fever, and chills were seen. Besides, some significant adverse effects were detected in physical exams, like lymphadenopathy (LAP), which was found in 0.3% and 1.1% of those who received Pfizer-BioNTech and Moderna vaccines, respectively.[8-10] In imaging modalities, numerous reports of ipsilateral local adenopathy were published by proceeding vaccination in the worldwide population. Therefore, ascertaining the nature of adenopathy and its relationship with other factors, and planning a roadmap is critical, especially in screening or follow-up of the cancerous patients, such as those with breast cancer (BC).[11,12]

A former study by Keshavarz *et al*. reviewed all cases with LAP following COVID-19 vaccination, which was a helpful guide for physicians.[13] Therefore, we intended to perform an updated review of LAP-associated COVID-19 vaccination by focusing on the relation to BC based on the recent studies.

METHODS

Search strategy

We searched various online data sources, including PubMed (Medline), Scopus, Embase (Elsevier), Web of Science, and Google Scholar, from January 1, 2019, to February 28, 2021, and updated on August 1, 2021. All types of studies, including original research studies, case series/reports, correspondence, and editorials were evaluated. Vaccinated cases, with all FDA or WHO-approved COVID-19 vaccines, in the studies presented with LAP after vaccination (after the first or second dosage) by various imaging modalities such as CT scan, MRI, mammography, Ultrasound, and also nuclear medicine modalities like PET/CT scan and PET/MRI were included. Duplicates, abstracts, preprint studies, articles reporting other adverse events of COVID-19 vaccines, and studies without available full texts were excluded. The keywords for the literature search included “COVID-19”, “coronavirus disease”, “Vaccine”, and “Vaccination”, “LAP”, “Adverse event*”, “Lymph node”, “Cancer, breast”, and “Lymphadenopathy”.

Data collection

Two independent reviewers evaluated the list of title abstracts and full texts of the included studies. A third reviewer further resolved the disagreements through consensus. Additionally, any remaining published studies were identified using citation tracking. The following data were extracted with a focus on the following information such as the first author’s name, region or country, type of study, patient’s characteristics, type of vaccine, a dosage of vaccine injection, size and location of LAP, appearance of some radiological findings like lymph node hilar fat and cortical thickening, and the type of imaging modality. Further, we reported a series of imaging findings from two studies,[14,30,34,35] with formal permissions to use or permissions under the Creative Commons Attribution-NonCommercial-No Derivatives License (CC-BY-NC-ND) (Figures 1, 2, 4, and 5).

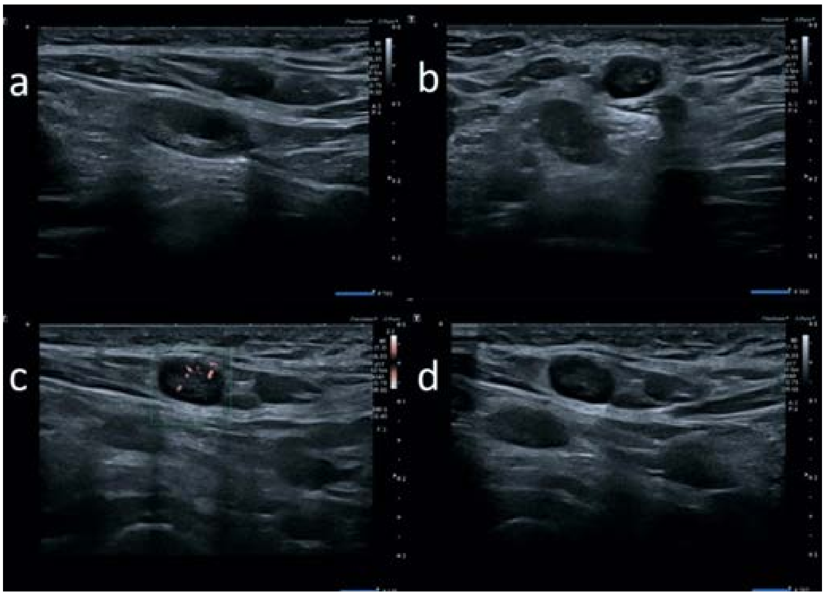

Figure 1. A 25-year-old female with unilateral left axillary adenopathy noted 5 days after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine in her left deltoid muscle. (a,b) B-mode sonogram image shows ovular lymph nodes with asymmetric cortex and dislocate hilum. (c) After 2 months, SMI image shows normal vascularization. (d) Cortical thickening appears uniform with normal hilum localization. Images obtained from Cocco *et al*.,[14] Biology, published online: July 12, 2021, and this study is an open access article distributed under the Creative Commons Attribution-NonCommercial-No Derivatives License (CC-BY-NC-ND) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

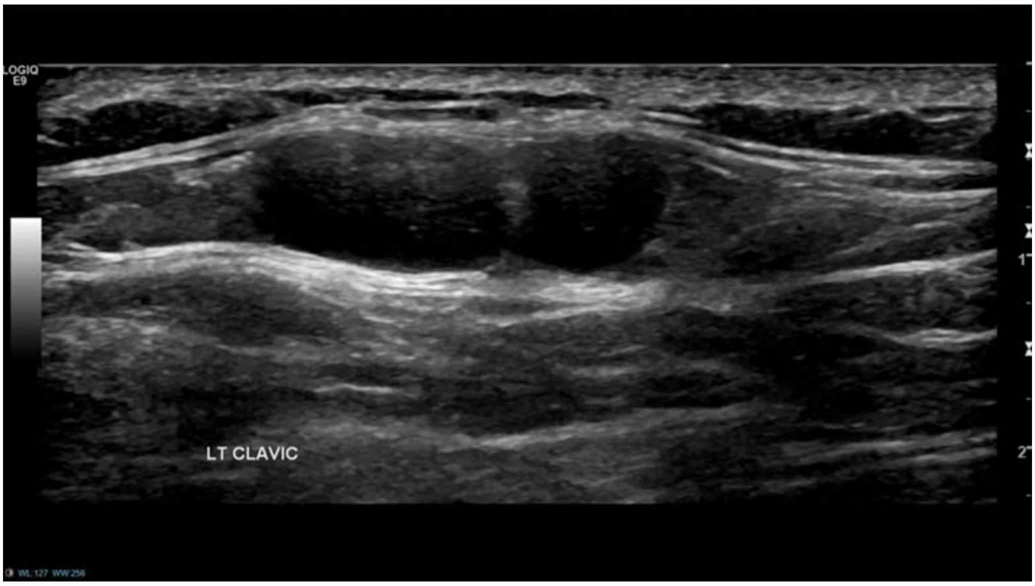

Figure 2. A 38-year-old woman, with no personal or family history of breast cancer, presented with a 4-week history of a palpable lump inferior to the left clavicle, which was first noticed approximately one week after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine in the left arm. Ultrasound of the left axilla and supraclavicular fossa (SCF) revealed normal-appearing axillary lymph nodes and a couple of lymph nodes up to 8mm in size in the area of interest, with appearances favoring benign reactive nodes. A bilateral mammogram showed no abnormalities. As the patient was due to have her 2nd vaccine dose in 5 weeks' time, she was advised to return for a 10-week follow-up ultrasound scan and clinical examination to ensure resolution. The patient reported that in the following weeks, the adenopathy progressively improved. Two days after receiving the 2nd vaccine dose, she again developed palpable SCF adenopathy that had disappeared completely by the time of her follow-up appointment. Permission to publish the images was obtained from Garreffa et al.[30], European Journal of Cancer, published online: October 11, 2021.

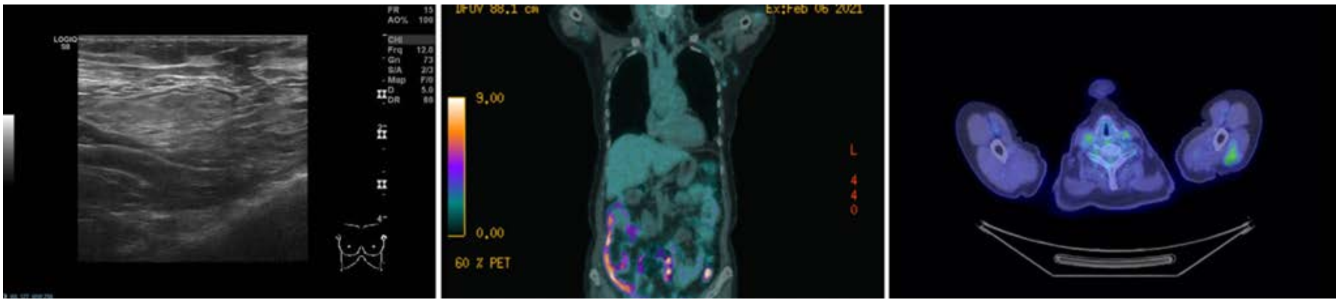

Figure 4. A 73-year-old female who was referred to the symptomatic breast clinic with a one-month history of a left-sided breast mass. Clinical examination revealed a 25mm suspicious breast mass and no clinically palpable axillary or supraclavicular lymph nodes. On breast imaging, the mass was also suspicious of malignancy, measuring 26mm on mammography and 24mm on ultrasound scan. Axillary ultrasound at that time demonstrated no lymphadenopathy (left). The breast biopsy showed evidence of squamous cell carcinoma (SCC). Due to the unusual histology, a whole-body PET-CT scan was performed to rule out primary SCC from other sites. This did not show evidence of another primary malignancy; however, clustered left axillary and subpectoral nodes, measuring <1cm, were identified. They were judged as presumably inflammatory in nature, although malignant infiltration could not be excluded (middle). There was also uptake noticed within the left deltoid muscle (right). The patient had the 1st dose of the AstraZeneca COVID-19 vaccine in the left arm one day prior to the PET-CT scan. The lymphadenopathy was considered likely to be vaccine-related and the patient underwent a left mastectomy and left sentinel node biopsy, which was negative for lymph node metastasis. Permission to publish the images was obtained from Garreffa *et al.*[34], European Journal of Cancer, published online: October 11, 2021.

RESULTS

Literature search

A total of 2128 studies were detected in the primary search. After removing duplicates, 73 articles were eligible and related to our inclusion criteria. Finally, 59 studies from the USA, UK, Italy, Germany, Portugal, Canada, France, Israel, Ireland, Egypt, Kuwait, and South Korea were included. The flow diagram of the study selection process is presented in Figure 3. This study reviewed a total number of 880 cases that had reactive LAP following the COVID-19 vaccination. All characteristics of different reported imaging approaches were investigated.

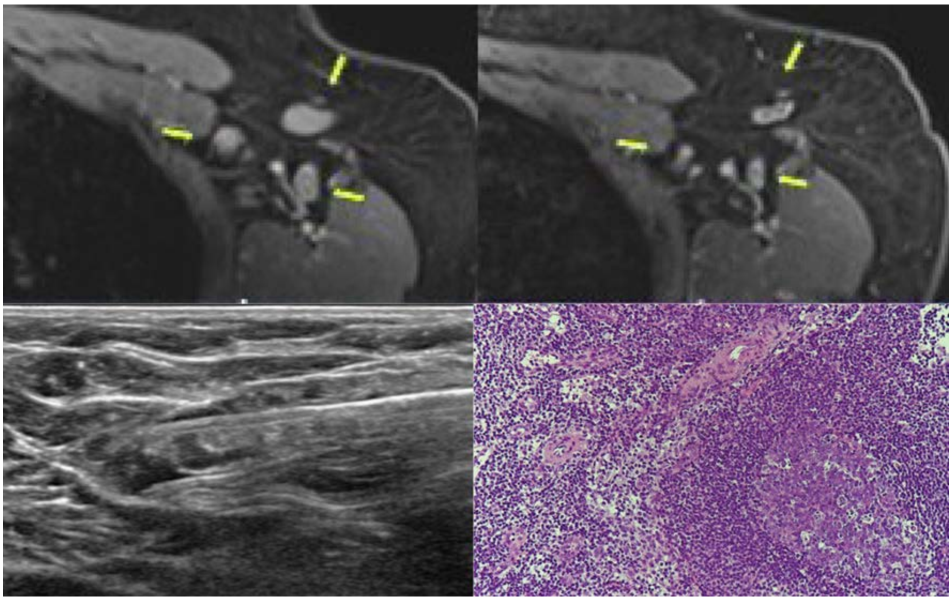

Figure 5. A 61-year-old woman with a history of right breast cancer with right axillary metastasis underwent her routine 5-year follow-up imaging studies after treatment. Multiple left axillary lymph nodes were observed in axillary level I (upper left), showing a significant increase in cortical thickness of lymph nodes compared with her previous breast MRI (upper right, arrows highlight the lymph nodes). She had received her first dose of Vaxzevria in the left arm 16 days before the breast MRI scan and 22 days before the breast ultrasound. Pathologic confirmation and ultrasound guided 14-gauge gun biopsy was performed (lower left), with a diagnosis of benign hyperplasia (lower right). The images were obtained from Lim *et al.*[35], Seminars in Oncology, published online: October 26, 2021, and this study is an open access article distributed under the Creative Commons Attribution-NonCommercial-No Derivatives License (CC-BY-NC-ND) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

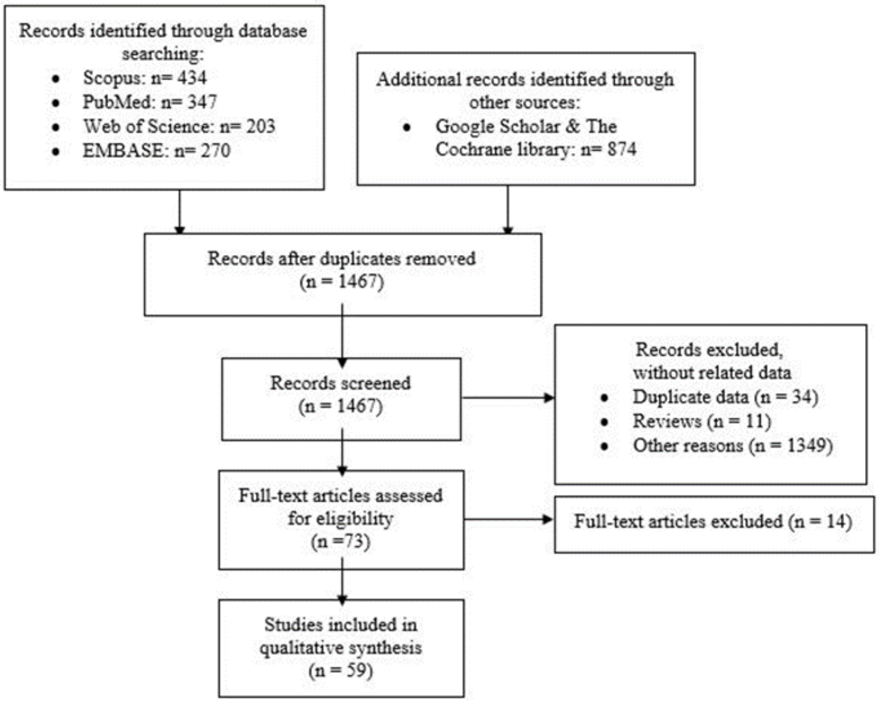

Figure 3. Flow diagram of the study selection process.

Patients' study

We reviewed 880 cases, including 412 (46.8%) females, 146 (16.6%) males, and 322 (36.6%) cases with unknown gender. In total, 193 (21.9%) cases had the history or active malignancy, including BC (n=47; such as triple-negative, HER2 positive, invasive ductal, breast focal lesion, localized or metastatic or had a positive family history of BC), hematologic malignancies (n=34), lung cancer/nodule (n=23; including localized or metastatic, and positive history), gastrointestinal cancers (n=17), genitourinary cancers (n=21), head and neck cancers (n=11), musculoskeletal cancer (n=2), melanoma (n=21), lymphoma (n=4, including Hodgkin and non-Hodgkin), and skin cancers (n=13, including Merkel cell carcinoma). In addition, 51 patients had particular conditions, including 47 patients with *BRCA* mutations, four patients with a history of immunotherapy, and one patient with a history of infection/inflammation (Table 1).

Table 1. Types of malignancies in patients with reactive LAP

Type of Malignancy		Current malignancies	History of malignancies	Positive family history
Breast cancer	localized	19	21	5
	metastatic		2	
Hematologic malignancies		34		
Lung cancer/nodule	localized	19	2	
	metastatic	2		
Gastrointestinal cancers		14	3	
Genitourinary cancers		19	2	
Head & neck cancers		11		
Musculoskeletal cancers	localized	1		
	metastatic		1	
Melanoma	localized	15	2	
	metastatic	4		
Lymphoma	hodgkin	2	1	
	non-Hodgkin		1	
Skin cancers		13		

Imaging findings

Mammography and Ultrasound

In the present study, the cases reviewed underwent ultrasound examination for various reasons in which screening for primary breast cancer in women constituted a significant part; in addition, previously treated cancer follow-up and sentinel lymph node investigation before sampling and seeking possible metastasis were other purposes. Histopathological evaluation was unremarkable, which did not reveal evidence of malignancy. The abnormal lymph nodes were seen in several anatomical locations. Among these, the left Axillary had the largest share, followed by the right axillary, supraclavicular, left infraclavicular, left subpectoral, and left low lateral neck. Among 157 patients whose lymph node size was reported, their size range was between 1.1 to 48mm. Local or diffuse cortical thickening was seen in most of them. The range of cortical thickness was 3.9 to 15mm, reported in 136 cases. Hypoechoic lymph nodes accounted for more cases, although hyperechoic lymph node was also observed. In addition, other cases were observed with lymph nodes without defined hilum, lymph nodes with increased vascularity, and lymph nodes with fat stranding. All of these are shown in detail in Table 2. It is important to note that the number of lymph nodes is not equal to the sum of patients because, in some patients, reactive lymph nodes were observed in more than one anatomical location.

All mammograms have been performed on women for various purposes, including initial breast cancer screening, previous cancer follow-up, and examination of a lump in the breast or axilla.

MRI

Magnetic resonance imaging (MRI) is another modality done in high-risk patients for BC screening that presented with a localized unilateral single left axillary, unilateral multiple axillaries, multilocal left axillary, mediastinal, and right hilar lymph nodes. In addition, the size range in observed abnormal lymph nodes was from 20mm to 24mm, and the range of cortical thickness was from 3 to 13mm. All of these are shown in detail in Table 2.

CT scan

Both axillary sides and left subpectoral reactive lymph nodes were observed in chest computed tomography (CT) as an accidental finding or during a targeted screening or diagnostic procedure. The minimum recorded size was 9.7mm, and the maximum lymph node size was 22mm. All of these are shown in detail in Table 2.

FDG PET/CT, MRI[18]

The most used modality among the reviewed studies was FDG PET/CT[18], which in most cases was used for the follow-up of cancer patients, and the hyperactive lymph node was found incidentally next to the principal target, but in some studies, it was applied entirely to find an abnormal lymph node after vaccination. The diversity of findings and the locations of the observed hyperactive lymph nodes were more distinct than in other modalities. However, the left axillary was still ranked first among various sites, right axillary, bilateral axillary, right and left supraclavicular, pectoral, subpectoral, interpectoral, and cervical. Even in one case, the external iliac and

Table 2. Distribution of studies with COVID-19 vaccinated-associated LAP according to the imaging modalities and findings

Imaging Modalities	First author, region (Ref)	Imaging findings	Location of LAP (N)
Mammography	Washington, USA (36) Lehman, USA (37) Mortazavi, USA (38) Duke, USA (39) Faermann, Israel (40)	Prominent Lt. axillary and intramammary LN	Lt. axillary (n = 36)
Ultrasound	Mortazavi, USA (38) Mitchell, UK (41) Ahn, USA (42) Hiller, Israel (43) Ozutemiz, USA (44) Brown A, UK (45) Granata, Italy (18) Dominguez, USA (46) Cardoso, Portugal (16) Abou-Foul, UK (47) Washington, USA (36) Mehta. USA (20) Becker, USA (48) Cellina, Italy (49) Duke, USA (39) Faermann, Israel (40) Garreffa, UK (50) DAuria, Italy (51) Cocco, Italy (14) Placke, Germany (22) Ahn, USA (42)	Unilateral single Lt. axillary LN (n = 140) Unilateral single Rt. axillary LN (n = 1) Unilateral multiple axillary LNs (n = 45) Unilateral single supraclavicular LN (n =1) Unilateral multi supraclavicular LNs (n =14) Unilateral multi infraclavicular LNs (n =1) Unilateral single subpectoral LN (n = 1) Multiple areas (axillary, supraclavicular, low lateral neck) (n = 4) Unilateral latrocervical site (n = 24) Diffuse cortical thickening (n = 28) Range of size: 1.1 mm to 48 mm that reported in 157 cases Range of cortical thickness: 3.9 to 15 mm that reported in 136 cases Hypoechoic LN (n = 5) Hyperechoic LN (n = 1) LNs w/o defined hilum (n = 21) LNs with increasing vascularity (n = 8) Fat stranding (n = 1)	Lt. axillary (n = 181) Rt. axillary (n = 1) Lt. supraclavicular (n = 18) Lt. infraclavicular (n = 1) Lt. subpectoral (n = 1) Lt. lateral neck (n = 27)
MRI	Ozutemiz, USA (44) Edmonds, USA (52) Mortazavi, USA (38) Lehman, USA (37) Bauckneht, Israel (53) Hiller, Israel (43) Duke, USA (39) Faermann, Israel (40)	Unilateral single Lt. axillary LN (n = 39) Unilateral multiple axillary LNs (n = 7) Lt. axillary, mediastinal, and Rt. hilar LNs (n = 1) Range of size: 20 mm to 24 mm that reported in 39 cases Range of cortical thickness: 3 to 13 mm that reported in 39 cases	Lt. axillary (n = 47) Lt. mediastinal (n = 1) Rt. hilar (n = 1)
CT	Lehman, USA (37) Canan, USA (54) Cardoso, Portugal (16) Dominguez, USA (46) Tu, USA (33) Brown, UK (45)	Unilateral single Lt. axillary LN (n = 2) Unilateral single Rt. axillary LN (n = 1) Unilateral multiple axillary LNs (n = 2) Several Lt. axillaries and subpectoral LNs (n = 2) Range of size: 9.7 mm to 22 mm that reported in 6 cases	Lt. axillary (n = 6) Rt. axillary (n = 1) Lt. subpectoral (n = 2)
^{18}FDG PET/CT	Nawwar, UK (55) Cohen, Israel (56) Weeks, USA (23) Ulaner, USA (57) Brown, UK (58) Steinberg, USA (59) Smith, USA (60) Singh, USA (61)Shah, UK (62) Schroeder, USA (63) Mitchell, UK (41) Lehman, USA (37) Eshet, Israel (21) Finnegan, Ireland (64) Doss, USA (65) Brown, UK (58) Bernstine, Israel (66)	Unilateral single Lt. axillary LN (n = 10) Unilateral multiple Lt. axillary LNs (n = 33) Unilateral single Lt. supraclavicular LN (n =23) Unilateral single Rt. axillary LN (n = 4) Unilateral multiple Rt. axillary LNs (n =2) Bilateral axillary LNs (n = 1) Bilateral supraclavicular (n = 1) Axillary LNs with unknown side (n = 224) Unilateral single subpectoral LN (n = 1) Rt. external iliac and inguinal lymph nodes (n = 1) Multiple areas (n = 342) Normal fatty hilum (n = 5) Range of size: 1.3 mm to 20 mm that reported in some cases Range of SUVmax: 0.4 to 9.4 that reported in 449 cases in ^{18}FDG PET	Lt. axillary (n = 43) Rt. axillary (n = 9) Unknown side axillary (n = 224) Lt. supraclavicular (n = 24) Rt. supraclavicular (n = 2) external iliac and inguinal (n = 1) Multiple areas (n = 342)

Imaging Modalities	First author, region (Ref)	Imaging findings	Location of LAP (N)
	Ahmed, Kuwait (67) Nawwar, UK (55) Eifer, Israel (68) Johnson, USA (69) Moghimi, Canada (70) Avner, Israel (71) Mclntosh, USA (72) Xu, USA (73) Fleury, France (17) McIntosh, USA (74) Adin, USA (75) Bass, USA (24) Schapiro, USA (15) Shin, South Korea (19) Hanneman, Canada (76) Schroeder, USA (63) Bauckneht, Italy (53)		
^{18}FDG PET/MRI		Multiple Lt. axillary LNs (n = 1) with SUVmax = 5.6, maximum diameter = 13 mm	Lt. axillary (n = 1)
CT Angiogram		Lt. axillary LN	Lt. axillary (n =1)
^{18}F-Choline PET/CT/ ^{18}C-Choline PET/CT	Nawwar, UK(55) Schroeder, USA (63)	Multiple Lt. axillary LNs (n = 2) Multiple Rt. axillary LNs (n = 2) Range of SUVmax: 0.6 ± 0.29 to 0.68 ± 0.38 reported in 3 cases in Choline PET	Lt. axillary (n = 2) Rt. axillary (n = 2)
^{68}Ga-DOTATATE PET/CT	Lu, USA (77) Weiler-Sagie, Israel (78) Brophy, USA (79)	Bilateral axillary and subpectoral LNs with SUV max 2.2-3.6 Unilateral axillary LNs (n = 2)	Lt. axillary (n = 2) Rt. axillary (n=1)

Note: Lt.: Left, Rt.: Right, LN: Lymph node

inguinal were other anatomical locations observed. Normal fatty hilum was seen in five patients. Only some of the studies registered sizes, with a great variety varying from 1.3mm to 20mm. Another variable seldom reported in these studies was SUVmax, which was also very varied and differed from 0.4 to 9.4. Besides, FDG PET/MRI^{18} was performed in two studies. One of them reported multiple left axillary lymph nodes with SUVmax 5.6 and a maximum diameter of 13mm. Other studies reported PET/CT examinations with F-Choline^{18} and Ga-DOTATATE^{68} derivatives were performed in a few studies; each study reported SUVmax: 0.6±0.29 to 0.68±0.38 and SUV max 2.2-3.6, respectively (Table 2).

Lymphadenopathy after vaccination

The axillary region has the greatest share of cases reported among abnormal lymph nodes after vaccination in the studies (n=540). Among them, the left side was more frequently involved than the right one. However, 215 cases have been registered without specifying the exact direction of the axillary involvement. The supraclavicular (n=44), interpectoral (n=39), subpectoral (n=7), pectoral (n=1), mediastinal (n=1), hilar (n=1), cervical (n=1), low lateral neck (n=1), inferior clavicular (n=1), and external iliac and inguinal (n=1) regions were the subsequent categories, respectively (Table 3).

DISCUSSION

This study reviewed 880 cases in 59 studies that reported LAP following COVID-19 vaccination. The review summarizes the subsequent principal findings from the literature. Keshavarz *et al*. reported the first imaging review study of LAP followed vaccination, gave highlights, and made recommendations for radiologists in the pandemic era regarding cancer screening and follow-up precautions.[13] By increasing the vaccination rate and its progress globally, and the importance of distinguishing between vaccine-associated LAP versus cancer-related LAP, there was a necessity to do a novel study. With increasing the abundance of articles published from different countries, this investigation focused on twelve countries, which spread over four continents. Although most of the documented data are from four countries previously studied, articles from other European countries such as Germany, Portugal, and France, Egypt from Africa, and Kuwait and South Korea from Asia can be found. Perhaps the more prominent share of the United States, Israel, and United Kingdom can be justified by the earlier and faster velocity of the vaccination.

Table 3. Distribution of the location of LAP according to type of COVID-19 vaccines

Vaccine type	Location of LAP	Number
Pfizer-BioNTech	Axillary	442
	Axillary & Supraclavicular	271
	Infraclavicular	1
	Lateral neck	25
	Pectoral & subpectoral	2
	Unknown site	13
Moderna	Axillary	34
	Supraclavicular	6
	Lateral neck	1
	Subpectoral	2
	Unknown site	3
Oxford-AstraZeneca	Axillary	31
	Unknown site	8
Sputnik V	Axillary	1
Johnson & Johnson/Janssen	Axillary	1
CureVac	Axillary	1
Unknown type	Axillary & subpectoral	7
	Axillary	30
	Supraclavicular	8
	Subpectoral	2
	Lateral neck	4
Total*	Axillary	540
	Axillary & supraclavicular	271
	Axillary & subpectoral	7
	Supraclavicular	14
	Infraclavicular	1
	Lateral neck	30
	Pectoral & subpectoral	6
	Unknown site	24
		893

*We have multiple locations of LAP in some of the patients

However, with the development of vaccination, we are witnessing new reports from other countries that makes it possible to generalize the complication to vaccines as a possible side effect in general.[16-19]

With this in mind, it should be noted that the variety of vaccines used has increased compared to the previous study, and this complication can no longer be considered specific to a particular type of vaccine with unique technology. Different types of vaccines have been much more diverse in the present study. Even though some vaccines used are unknown, at least six distinct brands such as Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, Sputnik V, Johnson & Johnson/Janssen, and CureVac have been reported. The most LAP presentation was reported following the second dose of Pfizer-BioNTech vaccination with more than 85% of all cases, which can be related to more people receiving this type.

Some recent studies have revealed that,[13,20] despite the Centers for Disease Control and Prevention's (CDC) recommendation for the decreasing days of LAP presentation after COVID-19 vaccines after the dosage of Pfizer-BioNTech and Moderna vaccines, detection is possible up to 6 weeks. By reviewing more articles in this study, this timeframe has grown even more and has risen to two months. Eshet *et al*. and Placke *et al*. have identified 50 days or more as the initial detection time of reactive LAP in imaging techniques.[21,22] In the study of Weeks *et al*., this figure goes up to sixty days.[23] They reported a patient undergoing FDG PET/CT for the follow-up of sigmoid adenocarcinoma, who showed bilateral axillary LAP two months after receiving the first dose of Moderna vaccine in the left deltoid and one month after receiving the second dose in the right side. It is important to note that due to the significant difference in SUVmax between these lymph nodes and abdominopelvic metastatic lymph nodes, the risk of malignancy in the axillary region is very scanty. In the study by Cocco *et al*., where the researchers followed up the patients with post-vaccination LAP by Ultrasound, two of the cases needed 60 days for node resolution.[14] A set of various radiologic parameters lead to confirming the reactive LAP diagnosis, including diffuse or focal cortical thickening, shape, and preserved hilar fat in the sonography, low or very low-grade uptake in PET/CT or PET/MRI scan, and sizes of prominent lymph nodes in imaging modalities.

The variety of imaging methods in the studies was significant, so different techniques were used to examine abnormal lymph nodes after the COVID-19 vaccination. In addition, they were conducted with multiple purposes such as screening and follow-up for cancers, palpable mass examination, and singularly in some of them to study the prevalence of LAP and its characteristics.

A recent review study by Keshavarz *et al*. reported that most LAP locations are in the axilla region, especially in the left and supraclavicular. The total number of positions has increased, so this phenomenon is also observed in the pectoral, subpectoral, interpectoral, mediastinal, and hilar areas.[13] Another extraordinary scene was external iliac and inguinal lymph nodes, which Bass *et al*. detected by increased uptake in FDG PET/CT three days after right thigh administration of the second Moderna vaccine dose.[24]

Several patients with different types of active cancer, history of cancer, positive family history of cancer, and patients at high risk for it, which involve the majority of BC patients, were considered in this review. It does not seem that there is a significant relationship between increased risk of cancer and post-vaccination LAP. Their total number did not exceed 240, which does not seem significant considering the cumulative number and the prevalence of this phenomenon in ordinary people. On the other hand, although the variety of features described in different imaging methods provide a distinct framework for diagnosing this complication, it does not eliminate the need for caution and shows the importance of an accurate memoir.

Cortical thickness and morphology of enlarged lymph nodes may be predictive of malignancy. Although HL *et al*. reported a cutoff of 5.4mm for cortical thickness with reasonable specificity for malignancy, we reviewed some cases that measured up to 22mm, which was secondary to vaccination. On the other hand, in this review, multiple cases had LAP without a defined hilum. So, the decision-making approach mandates multidisciplinary team work and collaboration among numerous specialties such as radiologists, surgeons, and others.

Meanwhile, due to the importance of timely diagnosis and an efficient approach to breast cancer to prevent the irreparable harms of diagnosis lag, family physicians as first-line providers must be aware of lymphadenopathy as the early symptom of breast cancer and must avoid vaccination-related LAP overrating.

Thus, vaccination in the contralateral arm of index cancer, the exact history of vaccination, transitions in the cortical thickness, and location of axillary LAP on imaging should all be considered for the best practice. The presence of extensive nodal involvement at levels II and III may be an indication of malignancy that requires more investigation.[25-31]

CONCLUSION

At first, being aware of the fact that reactive axillary LAP is a possible side effect of vaccination faced with radiologists is the principal point. It is necessary to avoid useless diagnostic imaging and invasive procedures. Besides, the importance of giving accurate memoirs and injection histories to the radiologist is even more apparent. Proper recording of patient information and its widespread and easy accessibility to the radiologist for more accurate interpretation and diagnosis of imaging findings, complete history, and information on vaccination of cancerous patients are important. Also, injecting the COVID-19 vaccine in a location far from the patient's primary cancer site, appropriate teamwork and suitable approach for the benefit of the patient, not delaying the screening, using diagnostic and treatment methods and follow-up for this reason in high-risk cases, and finally regular follow-up of post-vaccination LAP until complete resolution all can be considered as beneficial and necessary recommendations in this regard.

This review study can draw a broader perspective and a more comprehensive view on the problem for radiologists to proceed with the right approach at the right time without additional invasive measures, while not delaying the necessary action in high-risk patients at the same time.

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